Complete Summary

GUIDELINE TITLE

Use of neoadjuvant chemotherapy in transitional cell carcinoma of the bladder.

BIBLIOGRAPHIC SOURCE(S)

Genitourinary Cancer Disease Site Group. Winquist E, Waldron T, Segal R, Chin J, Lukka H. Use of neoadjuvant chemotherapy in transitional cell carcinoma of the bladder. Toronto (ON): Cancer Care Ontario (CCO); 2005 May 5. 26 p. (Practice guideline report; no. 3-2-2). [59 references]

GUIDELINE STATUS

This is the current release of the guideline.

The Guideline will expand over time to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Transitional cell carcinoma of the bladder

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology
Radiation Oncology
Surgery
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate whether neoadjuvant chemotherapy should be offered to patients with stage II or III bladder cancer before definitive local therapy with surgery and/or radical radiotherapy, with the intent of improving survival

TARGET POPULATION

Adult patients newly diagnosed with stage II or stage III transitional cell carcinoma of the bladder.

These guidelines are not intended for the following populations:

- Patients with only superficial transitional cell carcinoma of the bladder
- Patients with locally advanced bladder cancer that is surgically unresectable or metastatic
- Patients with bladder cancer of non-transitional histology

INTERVENTIONS AND PRACTICES CONSIDERED

Treatment

1. Neoadjuvant cisplatin-based combination chemotherapy
    - Methotrexate-vinblastine-doxorubicin-cisplatin (MVAC)
    - Cisplatin-methotrexate-vinblastine (CMV)
    - Gemcitabine-cisplatin
    - Dose-intense MVAC plus granulocyte-colony stimulating factor
2. Neoadjuvant single-agent cisplatin (Note: this is not currently recommended)

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Disease progression
- Toxicity

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE (January 1987 through March 2004, week 2), CANCERLIT (January 1987 through October 2002), and EMBASE (1980 through 2004, week 12) databases were searched for relevant papers. MEDLINE and CANCERLIT were searched using the following medical subject headings: "bladder neoplasms," "carcinoma, transitional cell," "chemotherapy, adjuvant," and "neoadjuvant therapy," EMBASE was searched using the following Excerpta Medica tree terms: "bladder tumor," "bladder cancer," "transitional cell carcinoma," "drug therapy," "chemotherapy," "antineoplastic agents," and "adjuvant therapy." In each database, those subject headings were combined with disease and treatment-specific text words: "bladder neoplasm," "bladder cancer," "bladder carcinoma," "carcinoma of the bladder," "transitional cell carcinoma," "neoadjuvant chemotherapy," "neoadjuvant," and "preoperative." Those terms were then combined with the search terms for the following publication types and study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, and controlled clinical trials.

In addition, the Cochrane Library databases (2003, Issue 4) and the conference proceedings of the American Society of Clinical Oncology (ASCO) (1990 through 2003) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guideline Clearinghouse (http://www.guideline.gov) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Eligibility Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. They were fully published reports or abstracts of randomized controlled trials (RCTs) or meta-analyses that:
    a. compared neoadjuvant chemotherapy and definitive local therapy (cystectomy and/or radical radiotherapy with or without concurrent chemotherapy) with local therapy alone in patients with stage II or stage III transitional cell carcinoma (TCC) of the bladder
    b. reported comparisons of overall survival and/or progression-free survival
2. They were systematic reviews or evidence-based practice guidelines that addressed the guideline question.

NUMBER OF SOURCE DOCUMENTS

Sixteen randomized controlled trials (in twenty-two publications) and 5 meta-analyses were eligible for inclusion and review.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Background

In the original guideline report completed in 2001, the Genitourinary Disease Site Group (GU DSG) narratively summarized the results of 14 randomized controlled trials (RCTs) of neoadjuvant chemotherapy and one meta-analysis performed by the Advanced Bladder Cancer Overview Collaboration (ABCOC) that pooled survival data from four of the 14 trials. The GU DSG did not perform their own meta-analysis of the trial data at that time because the majority of trials did not provide sufficient data to perform meta-analysis (seven of the 14 trials were either available only in abstract form or unpublished). The ABCOC meta-analysis has been updated twice, since the completion of the original guideline, to incorporate new trial data. The results of four more trials have been published since the last ABCOC update in 2001. With the full publication of those four additional trials, the GU DSG decided to conduct their own meta-analysis. The GU DSG was aware that a large individual patient data (IPD) meta-analysis of the neoadjuvant chemotherapy trials was in progress by the Medical Research Council (MRC). However, they decided to proceed with a pooled analysis of the published data because individual patient data reports can sometimes take years to complete. Results from the Medical Research Council individual patient data meta-analysis were published in mid-2003. The GU DSG meta-analysis was also completed around that time and was published in early 2004. The GU DSG meta-analysis has been updated since that publication to include updated data from two of the trials. The results of all five meta-analyses (ABCOC, Medical Research Council, and GU DSG) are summarized in the original guideline report.

Genitourinary Cancer Disease Site Group Meta-analysis Methods

The GU DSG considered overall survival and disease progression as the primary and secondary endpoints for meta-analysis, respectively. The GU DSG planned to pool published data on those endpoints for all trials and for particular subgroups of trials specified a priori.

Subgroup analyses were performed by type of chemotherapy: trials were categorized as either evaluating single-agent or combination chemotherapy. Exploratory analyses by type of local therapy (cystectomy versus other local therapies) and type of combination chemotherapy (regimens including anthracyclines versus those not) were also performed.

The hazard ratio (HR) is the most appropriate statistic for pooling time-to-event outcomes because it incorporates data from the entire survival curve and allows for censoring. When the HR and its associated variance were available, those statistics were extracted directly from the most recently reported trial results. Otherwise, the HR was estimated indirectly from other summary statistics (e.g., 95% confidence intervals [CI] or p values) or from data extracted from published Kaplan-Meier curves, using the methods of Parmar et al. If data were not provided from which HRs could be derived, the trial was not included in the meta-analysis. Chi-square tests were used to test for statistical heterogeneity among trials and to assess the consistency of treatment effect across different subgroups of trials. Use of a fixed-effect model was planned unless trial heterogeneity was apparent. The log-rank of observed minus expected number of deaths and the variance of each trial were combined across all trials to estimate an overall pooled HR. The pooled HR represents the overall risk of death associated with neoadjuvant chemotherapy plus local therapy compared with local therapy alone. HRs of 1.0 indicate no difference between treatment and control groups, HRs of less than 1.0 favour neoadjuvant chemotherapy, and HRs greater than 1.0 favour local therapy alone. Trial results were pooled using Review Manager 4.2.3 (Metaview © Update Software), which is available through the Cochrane Collaboration.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Since completion of the original guideline, considerably more data on combination chemotherapy has become available, prompting the Genitourinary Cancer Disease Site Group (GU DSG) to update and revise the original guideline report. In December 2003, the GU DSG reviewed the new evidence and developed a set of draft recommendations. The GU DSG members reached consensus that there is now sufficient evidence to recommend cisplatin-based combination chemotherapy prior to local therapy in patients with stages II or III bladder cancer. A variety of cisplatin-based chemotherapy regimens have been evaluated in randomized trials, but the majority of patients have been treated with either combination cisplatin-methotrexate-vinblastine (CMV) or methotrexate-vinblastine-doxorubicin-cisplatin (MVAC) for three cycles. Those regimens should be considered standards for neoadjuvant treatment until further data on other less toxic chemotherapy regimens (i.e., gemcitabine-cisplatin or dose-intense MVAC with granulocyte-colony stimulating factor [G-CSF]) in this setting are available. CMV and MVAC are associated with significant rates of nausea and vomiting, stomatitis, renal dysfunction, myelosuppression, and neutropenia in particular. In the two largest trials, the toxic death rates with CMV and MVAC were 1% and 0%, respectively. Therefore, neoadjuvant cisplatin-based combination chemotherapy should be

administered by a physician experienced in administering chemotherapy in those patients.

The GU DSG also discussed the timing of chemotherapy, namely whether physicians should administer chemotherapy neoadjuvantly versus adjuvantly. Presently, in terms of overall survival, the evidence is strongest for neoadjuvant chemotherapy. However, many oncologists prefer the adjuvant approach due to the inaccuracy of clinical staging of bladder cancer. Therefore, adjuvant chemotherapy following cystectomy is also a reasonable treatment option in these patients. Adjuvant chemotherapy is the subject of a separate guideline developed by the GU DSG. Patients should be presented with these treatment options, and an informed decision about the use of neoadjuvant chemotherapy should be made based on realistic expectations, individual preferences, and the perceived risks. As the absolute benefits of neoadjuvant chemotherapy are modest, patients should also be encouraged to participate in clinical trials whenever these are available.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 90 practitioners in Ontario (12 medical oncologists, 18 radiation oncologists, and 60 urologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on July 14, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Genitourinary Disease Site Group (GU DSG) reviewed the results of the survey.

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Thirteen of 14 members of the PGCC returned ballots. Eleven PGCC members approved the practice guideline report as written, and two members approved the guideline and provided suggestions for consideration by the GU DSG. One member suggested the GU DSG consider how the recommendations will be implemented into practice and resource implications since practitioner feedback indicated the wide use of gemcitabine-cisplatin. The other member suggested editorial changes be made to the Key Evidence section of the original guideline document.

The practice guideline has been approved by the GU DSG and by the PGCC.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Neoadjuvant cisplatin-based combination chemotherapy is recommended prior to radical cystectomy, radical radiation therapy (with or without concurrent chemotherapy), or preoperative radiotherapy and cystectomy for the purpose of improving overall survival and disease-free survival.
- The current state of the evidence does not permit a recommendation for an optimal cisplatin-based combination chemotherapy regimen. However, the largest neoadjuvant trials have used standard methotrexate-vinblastine-doxorubicin-cisplatin (MVAC) or cisplatin-methotrexate-vinblastine (CMV) for three cycles, and it is the opinion of the Genitourinary Cancer Disease Site Group that these regimens are reasonable treatment options. Less toxic regimens such as gemcitabine-cisplatin and dose-intense MVAC plus granulocyte-colony stimulating factor have not been evaluated in randomized trials in this setting.
- Neoadjuvant single-agent cisplatin chemotherapy is not recommended.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and meta-analyses. In cases where the data did not appear conclusive, recommendations were based on the consensus opinion of the group.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- In a meta-analysis based on individual patient data, the pooled hazard ratio for all trials (single-agent and combination) favoured neoadjuvant chemotherapy but was statistically non-significant (hazard ratio, 0.91; 95% confidence interval, 0.83 to 1.01, p=0.084). The results from a subgroup analysis showed that neoadjuvant combination chemotherapy (n=2116, from six trials) significantly improved overall survival compared with local therapy alone (pooled hazard ratio, 087; 95% confidence interval, 0.78 to 0.97; p=0.016) and was associated with a 13% reduction in the risk of death and a 5% absolute benefit at five years. The treatment effect was observed irrespective of the type of local treatment and did not vary between subgroups of patients. Although cisplatin-based combination chemotherapy was beneficial, there was no evidence to support the use of single-agent cisplatin (pooled hazard ratio, 1.15; 95% confidence interval, 0.90 to 1.47,

p=0.26). Disease-free survival, locoregional disease-free survival, and metastasis -free survival were also improved with combination chemotherapy in this meta-analysis.

- In the meta-analysis based on published data (n=2915, from 12 trials), the pooled hazard ratio for all trials (single-agent and combination) was statistically significant (hazard ratio, 0.88; 95% confidence interval, 0.81 to 0.97; p=0.008) and represents a 12% reduction in the risk of death with chemotherapy compared with local therapy alone. In the subgroup analyses performed by type of chemotherapy, combination chemotherapy (n=2538 from eight trials) was associated with a statistically significant 14% reduction in the risk of death compared with local therapy alone (pooled hazard ratio=0.86; 95% confidence interval, 0.78 to 0.94; p=0.002) or an absolute survival benefit of 7%. Single-agent cisplatin (n=377 from three trials) was not associated with a survival advantage (pooled hazard ratio, 1.11; 95% confidence interval, 0.86 to 1.43; p=0.41).

POTENTIAL HARMS

The toxicities of cisplatin-based combination chemotherapy include nausea and vomiting, neutropenic sepsis in at least 10% of patients, and death in at least 1% of patients.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Methotrexate-vinblastine-doxorubicin-cisplatin (MVAC) and cisplatin-methotrexate-vinblastine (CMV) chemotherapy are associated with high rates of some adverse effects. These effects should be discussed with patients, and treatment should be managed by physicians experienced in administering chemotherapy to those patients.
- These recommendations do not apply to patients with only superficial transitional cell carcinoma of the bladder, locally advanced bladder cancer that is surgically unresectable or metastatic or bladder cancer of non-transitional histology.
- This guideline does not address the topics of concurrent chemotherapy given with radiotherapy or adjuvant chemotherapy. Adjuvant chemotherapy is addressed in a separate guideline developed by the Genitourinary Cancer Disease Site Group.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Genitourinary Cancer Disease Site Group. Winquist E, Waldron T, Segal R, Chin J, Lukka H. Use of neoadjuvant chemotherapy in transitional cell carcinoma of the bladder. Toronto (ON): Cancer Care Ontario (CCO); 2005 May 5. 26 p. (Practice guideline report; no. 3-2-2). [59 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2005 May 5

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC), is a project supported by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Genitourinary Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Genitourinary Disease Site Group (GU DSG) disclosed potential conflict-of-interest information.

Four of the five guideline authors disclosed they had no actual or potential conflicts related to this practice guideline report.

GUIDELINE STATUS

This is the current release of the guideline.

The Guideline will expand over time to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Use of neoadjuvant chemotherapy in transitional cell carcinoma of the bladder. Summary. Toronto (ON): Cancer Care Ontario (CCO). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Winquist E, Kirchner TS, Segal R, Chin J, Lukka H. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. J Urol 2004;171:561-9.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on August 12, 2005. The information was verified by the guideline developer on September 13, 2005.

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